Remarks:

Applicant has carefully studied the final Examiner's Action mailed February 6, 2009. Applicant thanks the Examiner for their careful attention in reviewing the application. The amendments appearing above and these explanatory remarks are believed to be fully responsive to the Action. Accordingly, this important patent application is now believed to be in condition for allowance.

Status of the Claims

Claims 1-2, 4, 7, 10, 12-17 and 19 were pending in the Office Action mail dated February 6, 2009. New claims 20-30 have been added. The newly added claims are supported by the original specification and figures. Support for the added claims can be found at about page 4 of U.S. Patent Application 10/009,036, entitled, "Cell Therapy for Chronic Stroke", filed September 30, 2002, the contents of which were incorporated by reference in the present application. The referenced page includes the heading "SUMMARY OF INVENTION". The paragraphs to which the present amendment finds support are numbered [0010] to [0014]. Support is also found at about page 5 under the heading "DETAILED DESCRIPTION". The paragraphs supporting the present amendment are numbered [0024] through [0036]. Additional support for the present amendment is found at about page 11 with the referenced page including the heading "CLINICAL EXAMPLES". The paragraphs to which the present amendment finds support are numbered [0083] through [0093]. Therefore, claims 1-2, 4, 7, 10, 12-17, 19, and 20-30 are currently pending and under examination.

Claim Rejections – 35 U.S.C. §103(a)

The applicant acknowledges the recitation of 35 U.S.C. §103(a).

Weiss in view of Sanberg and Grabowski:

Claims 1, 2, 4, and 17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,851,832 to Weiss (hereinafter "Weiss") in view of Sanberg et al. (1997. Soc. Neurosci Abstr 23(1-2):346, abstract 140.9) and Grabowski et al. (1994. Exp Neural.

127(1):126-136). Applicant respectfully traverses this rejection on the grounds that (1) one or more elements are missing from the cited combination; (2) the cited references teach away from each other and thus the cited combination results in an absence of an articulated reasoning with some rational underpinning to support the legal conclusion of obviousness; and (3) at the time the invention was made, one of ordinary skill in the art could not have obtained predictable results from the combination of elements in the prior art.

The Office must have a factual basis to support a legal conclusion of obviousness when rejecting claims under 35 U.S.C. § 103.[1] The analysis of an obviousness rejection is based on several basic factual inquiries: "[(1)] the scope and content of the prior art are to be determined; [(2)] differences between the prior art and the claims at issue are to be ascertained; and [(3)] the level of ordinary skill in the pertinent art resolved."[2] In order to support a conclusion of obviousness, it must be shown that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success."[3]

In determining obviousness, "all words in a claim must be considered in judging the patentability of that claim against the prior art."[4] According to MPEP § 2143.03, when an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is also nonobvious.[5] "Rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."[6]

One or more elements for a prima facie case of obviousness is missing

The combined references fail to establish a *prima facie* case of obviousness as outlined by MPEP 2142 for reasons including that the combined references fail to teach or suggest all

---

[1] *In re Fine* 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).
[2] *Graham v. John Deere Co.,* 383 U.S. 1, 17 (1966); see also *KSR v. International Co. v. Teleflex Inc.,* 127 S.Ct. at 1734.
[3] *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.,* 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006).
[4] See MPEP 2143.03 – All Claim limitations Must be Considered – *citing in re Wilson* " 'All words in a claim must be considered in judging the patentability of that claim against the prior art.' *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)."
[5] MPEP 2143.03 citing *In re Fine* 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).
[6] MPEP 2143 citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) quoting In re Kahn, 441 F. 3d. 977, 988 (Fed. Cir. 2006).

claim limitations (see also MPEP 2143.03). In particular, the Weiss patent does not teach or suggest (1) the administration of at least 6 million hNT neuronal cells to a human who has undergone stroke; (2) the administration of hNT neuronal cells at least 3 hours post-stroke; (3) the administration of hNT neuronal cells to a plurality of brain sites; or (4) the administration of hNT neuronal cells at least 3 months post-stroke, and these shortcomings are not overcome by combining the teachings of Weiss with the teachings of Sanberg and Grabowski.

Weiss fails to teach the administration of at least 6 million hNT neuronal cells and Sanberg and Grabowski fail to resolve that deficiency

The Office rejects claims 1, 2, 4, and 17 under 35 U.S.C. § 103(a) as being unpatentable under Weiss in view of Sanberg and Grabowski. Claim 1 is directed to "[a] method of treating stroke in a human who has undergone a stroke at least three hours earlier, said method comprising delivering **at least 6 million viable hNT neuronal cells** to a plurality of brain area sites involved in the stroke." (emphasis added) The Office concedes on page 3 of the Office Action dated February 6, 2009 that the particular sections that discuss treatment of stroke in Weiss do not explicitly indicate the number of cells that should be transplanted when stroke is treated. On the same page, the Office points to example 45 of Weiss as being illustrative as to the amount of cells to be administered and indicates that between 50,000 to 150,000 cells can be used per animal. However, example 45 indicates that the stem cell progeny were transplanted into the brain of normal, healthy neonate or adult mice or Wistar or Sprague-Dawley rats. It should first be noted that the cells used in example 45 of Weiss, as cited by the Office, were not hNT cells but rather multipotent neural stem cell progeny that were formed from the neural tissue of mice. (emphasis added) The differences between murine stem cells and hNT cells would not indicate that the specific cell amount used for one type of cell would necessarily correlate with the specific cell amount used for the other type of cell. The hNT cells differentiate into neurons generating a uniform population of human cells whose neuronal fate is already specified but that also respond to the local environment by assuming cellular morphologies and processes appropriate to the region into which they are grafted. In contrast, neural stem cells can give rise to multiple lineages but they rely on local cues in the recipient nervous system to specify their phenotype. In many regions of the post-natal CNS, transplanted neural stem cells

differentiate into glia.[7] Each cell type has differing characteristics that makes their comparison with each other regarding effective treatment doses incorrect. Thus the cell numbers in example 45 for multipotent stem cells from mice would not necessarily translate into the cell numbers needed if using hNT cells in humans.

The Office uses the teachings of Sanberg to overcome the shortcomings of Weiss with respect to the use of hNT cells. Sanberg states that administration of between 20,000 and 40,000 hNT cells, with 40,000 cells being the optimal dose, is effective to restore behavioral functions in ischemic rats. According to the Office, this would lead one of ordinary skill in the art to determine that the optimal dose would be at least 10 million hNT cells (as calculated by the Office in regard to the Sanberg reference on page 5 of the Office Action), not at least 6 million hNT cells as recited in the present application. The Office has offered no other evidence as to why the selection of at least 6 million hNT cells would be obvious. In the present case, the applicant was the first to conduct in vivo experiments on human stroke patients using hNT cells as treatment. The applicant based their selection of at least 6 million cells as the optimal dose on actual results from their *in vivo* experiments conducted on human stroke patients. The 10 million cells used in Sanberg is almost twice the amount of cells that were proven effective in the present application. As discussed in the next section, applicant maintains that the Weiss and Sanberg references cannot be combined given that they expressly teach away from their combination.

The Office concedes on page 3 of the Office Action dated February 6, 2009 that Sanberg does not explicitly teach administration of at least 6 million cells nor does Sanberg teach administering the cells to humans. In fact, the Office has conceded that neither Weiss nor Sanberg nor Grabowski explicitly teach administration of cells to humans.[8] There is no reason to conclude, and the Office offers no evidence, that the number of cells affected as a result of ischemic injury would be proportionately related to the weight of the human/animal in question. If one of ordinary skill in the art were to follow the reasoning suggested by the Office as to the amount of cells to be administered to a human suffering from stroke, then one could reasonably assume that the amount of cells needed would increase proportionately with the patient's body weight. The Office has not articulated a basis for assuming that the amount of cells needed to

[7] Watson, D.J. et al. "Genetically Modified NT2N Human Neuronal Cells Mediate Long-Term Gene Expression as CNS Grafts In Vivo and Improve Functional Cognitive Outcome Following Experimental Traumatic Brain Injury", *Journal of Neuropathology and Experimental Neurology,* (2003) Vol 62(4):368-380 at 368.
[8] Office Action dated February 6, 2009 at page 3.

treat a human with stroke is proportionately related to their body weight. Given both that the references cannot be combined due to the fact that they teach against their combination as well as the fact that the two references use different cell types whose effective treatment dose cannot be compared, there is no motivation to combine the references and the element of administering at least 6 million hNT cells to a human is missing from the cited combination, therefore the Office has failed to establish a prima facie case of obviousness.

Second, the stem cells used by Weiss in this example were transplanted into the brains of normal animals, not animals that had undergone stroke. Example 45 indicates that the stem cell progeny were transplanted into the brain of normal, healthy neonate or adult mice or Wistar or Sprague-Dawley rats. (emphasis added) The lesions in the brain of stroke victims may interact with the cells in a different way than if the cells were transplanted into a normal brain. In fact, on page 126, Grabowski states:

> "Implantation site is of importance, since there is ample evidence that grafted neurons survive better and produce more fiber outgrowth in regions which they normally innervate and **may sometimes be stimulated by lesions to the host brain**." (emphasis added)

This excerpt from Grabowski indicates that neuronal activity of transplanted cells may be different in brains that have lesions as opposed to a normal healthy brain. Given that the stem cell progeny in Weiss were transplanted into healthy normal brains as opposed to brains with lesions, the results and cell number used in example 45 of Weiss are inapplicable to the present application. As shown in the next section, while Sanberg teaches the administration of hNT cells to rats that have undergone stroke, it is improper to combine these references given that they teach against their combination. Weiss fails to teach the administration of at least 6 million hNT cells to a human who has undergone stroke and Sanberg and Grabowski fail to resolve that deficiency therefore there can be no finding of obviousness.

Third, the Office notes that at column 64, lines 12-22, Weiss discloses treatment of stroke. However, this is a hypothetical example since no actual studies were conducted on stroke victims. Given that actual studies were not conducted, it is unknown from the teachings of Weiss whether or not stroke can be treated through the administration of cells. In fact, the Office concedes that the particular sections that discuss treatment of stroke do not explicitly indicate the number of cells that should be transplanted when stroke is treated.[9] The cell numbers in example

[9] Office Action dated February 6, 2009 at page 3.

45 of Weiss cited by the Office are inapplicable to the present invention given the differences in cell type, species, age, disease state, cell source, etc. The Office cites column 63, line 63 through column 64, line 12 as representative of an example of an experiment that induced ischemia. The heading, as conceded by the Office is entitled "Cardiac Arrest". The lesions in this experiment are said to be representative of damage observed after cardiac arrest, NOT stroke. Given that "stroke" and "cardiac arrest" are listed as separate headings for separate examples, the example for "cardiac arrest" is not contemplated by Weiss as being a treatment for stroke. If the inventors had intended to address stroke with cardiac arrest, they would not have listed each as a separate example. There are too many parameters to alter in comparing the cell number of example 45 of Weiss with the present application given the differences between cell source, species, age, cell type, disease state, etc. Given that Weiss uses mouse stem cells, not hNT cells, as well as the facts that the cells in the cited example are transplanted in normal, healthy brains of rodents and no actual studies were conducted on animals with stroke let alone humans suffering from stroke, the cell number cited in example 45 of Weiss is inapplicable to the present invention. Sanberg fails to resolve the deficiencies of Weiss and given the fact, as shown in the next section, that the references teach away from their combination, there can be no finding of obviousness.

In conclusion, Weiss fails to teach the administration of at least 6 million hNT cells to a human who has undergone stroke and Sanberg and Grabowski fail to resolve that deficiency, therefore there is a failure to teach each and every element of the claims in question and a finding of obviousness cannot be found.

Weiss fails to teach waiting at least 3 hours before delivering treatment and Sanberg and Grabowski fail to resolve that deficiency

One of the elements of claim 1 is to delay delivery of the hNT neurons until at least 3 hours post-stroke. Neither Sanberg nor Weiss teaches waiting at least 3 hours post-stroke for delivery of cells. In fact, neither reference mentions delaying delivery of the cells for any time period at all. As stated above, the Grabowski reference teaches waiting at least 5-7 days after the lesion occurs before doing graft implantation. Grabowski states on page 135:

> …"mechanisms underlying ischemic brain damage may have a negative influence on the transplanted cells and explain the **poor survival when grafting is performed soon after the ischemic result**." (emphasis added)

> ""The results, which demonstrated significantly **poorer graft survival** when the tissue was **implanted 1 day after artery occlusion** then after 5-56 days following lesion…are consistent with the notion that neuro-trophic support from a damaged host cortex requires **several days to develop**."

Given the above excerpt, Grabowski does not teach waiting at least 3 hours after brain damage and in fact teaches away from waiting for any time period shorter than 5 days as discussed previously. Grabowski cites specific results that indicate delivering treatment prior to 5 days post-stroke was unsuccessful in their studies. Since Grabowski fails to teach waiting for time periods less than 5 days and in fact teaches against delaying treatment for time periods of less than 5 days, it does not resolve the deficiencies of Weiss and Sanberg. The cited combination fails to teach each and every element of the claims in question and consequently cannot be said to render the present invention obvious.

Weiss does not teach the administration of hNT neuronal cells to a plurality of brain sites and Sanberg and Grabowski fail to resolve that deficiency

Claim 1 is directed to "[a] method of treating stroke in a human who has undergone a stroke at least three hours earlier, said method comprising delivering at least 6 million viable hNT neuronal cells to a **plurality of brain area sites** involved in the stroke". (emphasis added) Claim 17 is directed to, "[a] method of replacing in a human's nervous system nerves lost to a stroke, the method comprising administering to the human a sterile composition of at least 6 million hNT neuronal cells to a **plurality of brain sites**." (emphasis added) As shown above, both independent claims 1 and 17 of the present application expressly recite delivering hNT cells to a plurality of brain sites. As conceded by the Office in the Office Action dated February 6, 2009, neither Grabowski, nor Weiss, nor Sanberg teach delivery of cells to "a plurality of brain sites" as recited in claims 1 and 17.[10] The Office specifically states:

> "However, **Weiss…does not explicitly teach 'a plurality of brain area sites'**, as recited in claims 1 and 17… (emphasis added)[11]
>
> "…however **Sanberg does not explicitly teach…a plurality of sites** as recited in claims 1 and 17…" (emphasis added)[12]
>
> "However **Grabowski does not explicitly teach 'a plurality of brain area sites'** as recited in claim 1." (emphasis added)[13]

[10] Office Action dated February 6, 2009 at pages 3-4.
[11] Office Action dated February 6, 2009 at page 3.
[12] Office Action dated February 6, 2009 at pages 3-4.

The delivery of hNT cells to a plurality of brain sites is an express feature of the claims in question that the combination of the cited references does not produce. The Office has conceded that none of the cited references teach the administration of cells to a plurality of brain area sites as directed in independent claims 1 and 17 of the present application. Given that Weiss in view of Sanberg and Grabowski fails to teach the element of delivery of cells to a plurality of brain sites, each and every element of the claims in question is not taught by the combination of references and thus a finding of obviousness cannot be found.

Weiss fails to teach waiting at least 3 months post-stroke before administering treatment and Sanberg and Grabowski fail to resolve that deficiency

Claim 4 is directed to "the method of claim 1 wherein the stroke has taken place at least 3 months earlier." As conceded by the Office on pages 3 and 4 of the Office Action dated February 6, 2009, none of the references teaches waiting at least 3 months post-stroke before administering treatment. As stated above, both Weiss and Sanford fail to teach any delay in treatment. The Office uses the Grabowski reference to provide the element of delay in treatment, however Grabowski does not teach waiting at least 3 months before administering treatment as indicated in claim 4 of the present application. In fact, as shown below, Grabowski specifically teaches away from waiting 3 months post-stroke to administer treatment. Grabowski, as recognized by the Office, teaches waiting at least 5-7 days after the lesion occurs before doing graft implantation.[14] In addition, Grabowski places an upper limit on the delay period by stating that previous studies have found that a delay of 30-60 days after lesion was unsuccessful. These limits proposed in Grabowski, when taken together, propose a range of delay of 5-60 days before administering treatment. Clearly the 3 month (90 day) delay that is indicated in claim 4 falls outside of the range taught in Grabowski. Given that Weiss, in view of Sanberg and Grabowski, fail to teach the element of delaying treatment for at least 3 months, the combination of references fails to teach each and every element of the claims in question to yield the present invention and thus a finding of obviousness cannot be found.

---

[13]Office Action dated February 6, 2009 at page 4.
[14] Office Action dated February 6, 2009 at page 4.

In conclusion, for the foregoing reasons, Weiss in view of Sanberg and Grabowski fails to teach each and every element of the claims in question and thus a prima facie case of obviousness has not been established.

The cited references teach away from their combination

MPEP 2145 provides that it is improper to combine references where the references teach away from their combination.[15] "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."[16] "Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit the other."[17] One may rebut a prima facie case of obviousness by showing that the art, in any material respect, teaches away from the claimed invention.[18]

Claim 1 of the present application is directed to, "[a] method of treating stroke in a human who has undergone a stroke at least three hours earlier, said method comprising delivering at least 6 million **viable hNT neuronal cells** to a plurality of brain area sites involved in the stroke." (emphasis added) Weiss specifically teaches a method for the *in vitro* culture and proliferation of multipotent neural stem cells as well as the use of these cells and their progeny as tissue grafts. An express feature of claim 1 of the present application is the use of hNT neuronal cells for treatment of stroke in humans. Weiss does not teach the feature in claim 1 of using hNT neuronal cells and in fact, Weiss expressly teaches away from the use of hNT neuronal cells. At column 9, lines 16-30, Weiss states:

> "A **human teratocarcinoma-derived cell line, NTera 2/cl.D1**, with a phenotype resembling CNS neuronal precursor cells, can be induced to differentiate in the presence of retinoic acid. However, the differentiated cells are restricted to a neuronal phenotype. While these types of cells are able to generate a large number of cells for screening the effects of exogenous agents on cell survival or function, the **limited number of these types of cell lines, the limited number of phenotypes that they are able to generate and the unknown nature of their immortalization** (which may effect the function of the cells in an

[15] MPEP 2145 – References Cannot Be Combined Where Reference Teaches Away from Their Combination – citing *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).
[16] *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994).
[17] MPEP 2143.01 – Where the Teachings of the Prior Art Conflict, the Examiner Must Weigh the Suggestive Power of Each Reference- citing *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991)
[18] *In re Geisler,* 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

undefined manner) **makes *these types of cell lines less than ideal* for in vitro models of neural function and discovery of novel therapeutics**." (emphasis added)

In addition, Weiss states at column 5, lines 58-67 and column 6, lines 1-12:

> "Another source of tissue for neurotransplantation is from cell lines. Cell lines are immortalized cells which are derived either by transformation of normal cells with an oncogene or by the culturing of cells with altered growth characteristics in vitro. Such cells can be grown in culture in large quantities to be used for multiple transplantations. Some cell lines have been shown to differentiate upon chemical treatment to express a variety of neuronal properties such as neurite formation, excitable membranes, and synthesis of neurotransmitters and their receptors. Furthermore, upon differentiation, these cells appear to be amitotic, and therefore non-cancerous. However, **the potential for these cells to induce adverse immune responses, the use of retroviruses to immortalize cells, the potential for the reversion of these cells to an amitotic state, and the lack of response of these cells to normal growth inhibiting signals make *cell lines less than optimal* for widespread use**." (emphasis added)
>
> "The progeny of multipotent neural stem cells…are a particularly suitable cell line as the cells have not been immortalized and are not of tumorigenic origin."[19]

As shown by the above excerpts, Weiss teaches against the use of cell lines in general and specifically against the use of human teratocarcinoma derived cell lines such as hNT cells. Weiss lists the limitations of using cell lines, in particular human teratocarcinoma derived cell lines, and thus discourages the use of cell lines for neurotransplantation. Weiss criticizes and discredits the use of cell lines and therefore discourages their use in the treatment of stroke as recited in claim 1 of the present application. As stated previously, a prima facie case of obviousness can be rebutted by showing that the art, in any material respect, teaches away from the claimed invention.[20] Given that Weiss specifically teaches against the use of hNT cells while the present invention expressly teaches the use of hNT cells, there can be no finding of obviousness.

Similarly, Weiss and Sanberg cannot be combined to form the present invention given that the references teach away from their combination. As stated above, Weiss teaches away from the use of cell lines, particularly human teratocarcinoma derived cell lines such as hNT cells. In contrast, Sanberg expressly teaches the use of human embryonal teratocarcinoma cell-line derived neurons (hNT cells). The Office suggests that by substituting the use of hNT cells, as taught by Sanberg, into the teachings of Weiss, one of ordinary skill in the art would achieve the present invention. The Office states:

---

[19] US Patent 5,851,832 to Weiss et al. at column 23, lines 6-13.
[20] *In re Geisler,* 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

> "It would have been obvious to one of ordinary skill in the art to modify the methods of Weiss, who teaches treatment of stroke by administering neural stem cells and indicates that such treatments will also be effective in humans, by substituting the hNT cells of Sanberg and by waiting at least 5-7 days, as taught by Grabowski."[21]

As stated previously, "[i]t is improper to combine references where the references teach away from their combination."[22] In this case, the teachings of Weiss and Sanberg are in opposition. Since Weiss expressly teaches against the use of hNT cells, it would be improper to substitute the use of hNT cells as taught by Sanberg into the teachings of Weiss as proposed by the Office. Since these teachings are in opposition with each other, there is no motivation to combine the references. Given that references that teach away from each other cannot be combined to form an obviousness rejection, the Office has not articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.

Grabowski is used by the Office to overcome the limitation of independent claim 1 as to delivering treatment at least 3 hours post-stroke. Grabowski teaches waiting at least 5-7 days after the lesion occurs before doing graft implantation. Grabowski states on page 135:

> …"mechanisms underlying ischemic brain damage may have a negative influence on the transplanted cells and explain the **poor survival when grafting is performed soon after the ischemic result**." (emphasis added)

> ""The results, which demonstrated significantly **poorer graft survival** when the tissue was **implanted 1 day after artery occlusion** then after 5-56 days following lesion…are consistent with the notion that neuro-trophic support from a damaged host cortex requires **several days to develop**." (emphasis added)

Grabowski teaches away from delivering treatment for any time period less than 5 days as evidenced by their unsuccessful results when implantation occurred soon after the ischemic result. Based on Grabowski, one skilled in the art would be discouraged from administering treatment at any time period less than 5 days based on the failures of graft survival soon after the ischemic result. An express feature of the present invention is the delivery of treatment at least 3 hours post stroke. Since Grabowski teaches against delivering treatment at time periods less than 5 days, it does not resolve the deficiencies of Weiss and Sanberg and thus the cited combination does not produce the present invention. Given that Grabowski teaches away from the featured element of claim 1 of the present application of delivering treatment at least 3 hours post-stroke,

---

[21] Office Action dated February 6, 2009 at page 4.

[22] MPEP 2145 – References Cannot Be Combined Where Reference Teaches Away from Their Combination – citing *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

the Office has not articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.

In addition, Grabowski is cited by the Office in view of Weiss and Sanberg to overcome the limitation in claim 4 of the present application of administering treatment at least 3 months post-stroke. The Grabowski reference, as recognized by the Office, teaches waiting at least 5-7 days after the lesion occurs before doing graft implantation.[23] In addition, Grabowski states at page 126:

> "The host brain environment seems to be most hospitable around **3 weeks** after arterial occlusion." (emphasis added)

Also, at page 135, Grabowski notes that:

> "Previous work has suggested that implants of frontal cortex can improve acquisition of spatial alternation behavior in rats with medial frontal cortex lesions if graft surgery is conducted 7 or 14 **but not 30 or 60 days after lesion**" (emphasis added)

The teachings of Grabowski and the present application are in opposition given that claim 4 of the present application expressly dictates administering treatment at least 3 months post-stroke, while, in contrast, Grabowski teaches that 3 weeks post-brain injury is the preferred time period for implantation with 30-60 days post-brain injury being unsuccessful. Clearly 3 months (90 days) is past the time points of 30-60 days post-injury that are cited by Grabowski as being unsuccessful. One skilled in the art would be discouraged from administering treatment at least 3 months post stroke given the teachings of Grabowski. Since Grabowski teaches away from administering treatment at least 3 months post-stroke, there is no motivation to combine Weiss and Sanberg with Grabowski to arrive at the present invention and therefore a legal conclusion of obviousness cannot be supported.

In conclusion, given that references that teach away from the claimed invention cannot be used to form an obviousness rejection, the Office has not articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.

Given the state of the art at the time, the combination of references would not yield predictable results

[23] Office Action dated February 6, 2009 at page 4.

A *prima facie* case of obviousness requires that "all of the claimed elements must be known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one in ordinary skill in the art."[24] "Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made."[25]

"For a prior-art reference, or a combination of references, to render a claimed invention obvious, one of ordinary skill in the art at the time the invention was made must have expected a reasonable chance of success in applying the teachings of the references to arrive at the claimed invention."[26] "While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure." [27]

The Office points to the Kleim article as indicating that rat models of stroke, such as those used by both Weiss and Sanberg, are generally accepted in the field.[28] The Office concedes that the reference does point out certain limitations of the rat models and also concedes that the rodent models of stroke are imperfect.[29] The Office also states that some of the treatments which are effective in treating stroke in rodents are also effective in humans.[30] It is noteworthy that the Office states that **some** of the treatments for stroke are successful in humans, not that **all** of the treatments conducted on rodents are successful in humans. This statement by the Office acknowledges that there are limitations in translating rodent studies to treatment in humans. Kleim states:

> "Both basic and clinical scientists must also bear in mind that animal models of stroke are not designed to mirror the human condition nor provide specific details on how therapy should be conducted in the clinic.

---

[24] MPEP 2143.02 – Reasonable Expectation of Success Is Required; see also *KSR v. International Co. v. Teleflex Inc.,* 82 USPQ2d 1385, 1395 (2007); *Sakraida v. AG Pro, Inc.* 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.,* 396 U.S. 57, 62-63, 163 USPQ673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.,* 340 U.S. 147, 152, 87 USPQ 303, 306 (1950).
[25] *Ex parte Erlich,* 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986)
[26] PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1360, 83 U.S.P.Q.2d 1289, 1301–02 (Fed. Cir. 2007), cert. denied, 2008 WL 102402 (U.S. 2008).
[27] Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp. 320 F.3d 1339, 1354 (C.A.Fed. (N.J.),2003) citing *In re O'Farrell,* 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed.Cir.1988) and *In re Rinehart,* 531 F.2d 1048, 1053-54, 189 USPQ 143, 148-49 (CCPA 1976).
[28] Office Action dated February 6, 2009 at page 6.
[29] Office Action dates February 6, 2009 at page 6.
[30] Office Action dated February 6, 2009 at page 5.

> Rather, they serve to identify fundamental neural and behavioral principles of recovery that are readily observable in the laboratory and can be used to guide the development of novel clinical therapies."[31]

The applicant is not asserting that rodent studies are not useful for any purpose, but rather that they should not be used to provide specific details as to how therapy can be conducted in humans. As stated above, rodent models are useful to identify certain principles of recovery, however they should not be used to provide specific details on how therapy should be conducted in the clinic as the Office is suggesting in the present case.

The Office indicates that the Kleim article teaches the appropriate nature of the rodent MCA occlusion model and notes that the reference cites articles dating back to the mid-1980's as providing detailed instructions on how to perform the model.[32] The applicant does not question how to perform the model or when the model was put into use but rather questions its applicability in supplying specific details on how therapy should be administered to human stroke victims given the differences in brain composition between humans and rodents. The Office states on page 6 of the present Office Action that rodent stroke models were generally accepted in the art and cites the Carmichael reference from page 398 to 400. On page 399 of the cited reference, Carmichael states:

> "…the most common forms of human stroke are not malignant infarctions. These most common human strokes are approximately an order of magnitude smaller and are all associated with some degree of recovery. In comparing these numbers from rodent and human stroke, it is clear that there is a risk that many studies of MCAo in rodents, and particularly in the mouse, are not modeling the usual cases of human stroke, but are modeling malignant infarction… **rodent models of cell death in stroke produce very large infarcts that may not model the most common, and treatable, human strokes**."[33] (emphasis added)

Given that the rodent models at the time of the present application were not modeling the most common human strokes, one of ordinary skill in the art would not expect predictable results when administering treatment to humans afflicted by stroke.

---

[31] Kleim, J.A. et al. "Rat Models of Upper Extremity Impairment in Stroke" *Institute for Laboratory Animal Research Journal* (2007) Vol. 48(4):374-384 at 375.
[32] Office Action dated February 6, 2009 at page 6.
[33] Carmichael, S. T., "Rodent Models of Focal Stroke: Size, Mechanism and Purpose", *NeuroRX: The Journal of the American Society for Experimental NeuroTherapeutics*, 2:396-409 at 399.

In addition, several post-filing articles have indicated that even years after the present application, the results from animal models for stroke cannot necessarily be equated to humans as shown in the excerpts below:

> "While most of animal stroke models used in preclinical neuroprotection studies are MCA occlusion models, patients enrolled into clinical trials often include infarcts of diverse brain regions. Thus, some animal models may be poor predictors of clinical trial results. Another factor that may play a role in the discrepancies between preclinical and clinical study outcomes is the difference in the composition of brain between rodents and humans."[34]

> "Unfortunately, there are no corroborating animal models of chronic stroke to investigate transplantation several months after focal ischemia. Few outcome measures exist for animals with chronic stroke infarcts. Furthermore, functional recovery in animals cannot be easily equated across studies or related to humans."[35]

As shown from the above references, even years after the filing of the present application, rodent models of stroke do not produce predictable results when applied to human stroke victims. While the studies conducted on rodents in the post-filing references cited above may be useful in determining if the use of cells may be beneficial to humans, the actual cell amount and type needed to effectuate a successful response in humans was not predictable at the time of the present application from the combination of the Weiss, Sanberg, and Grabowski references cited by the Office. Applicant was the first to demonstrate that it was possible to safely implant hNT neurons into the basal ganglia of patients with stroke. None of the references cited by the Office conducts actual studies on human stroke patients. Given the difference in complexity between the human and rodent brains as well as the limitations (which were conceded by the Office) of the rodent models of stroke, it is unlikely that one of ordinary skill in the art would obtain predictable results when determining the effectiveness of cell treatment in humans at the time of the present application. Therefore, since none of the references teach a method of treatment for stroke in humans and there is no motivation to combine the references to obtain predictable results, there can be no finding of obviousness.

---

[34] Cheng, Y.D. et al. " Neuroprotection for Ischemic Stroke: Two Decades of Success and Failure" *NeuroRX: The Journal of the American Society for Experimental NeuroTherapeutics*, (2004) 1:36-45 at 41.

[35] Savitz, S.I., et al., "Cell Therapy for Stroke", *NeuroRx: The Journal of the American Society for Experimental NeuroTherapeutics",* (2004) 1:406-414 at 407.

For the foregoing reasons it is submitted that the Office has not made a *prima facie* case of obviousness as required under 35 U.S.C. § 103(a). It is therefore respectfully requested that the rejection of claims 1, 2, 4, and 17 under 35 U.S.C. § 103(a) be withdrawn.

Sanberg in view of Weiss and Uchida:

Claims 7, 10, 12-17 and 19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sanberg et al. (1996. Soc. Neurosci. Abstr. 22(1-3):578, abstract 232.9) in view of U.S. Patent 5,851,832 to Weiss et al. (hereinafter "Weiss") and Uchida et al. (1995. Exp. Neurol 132:194-208). Applicant respectfully traverses this rejection on the grounds that (1) the cited references teach away from each other and thus the cited combination results in an absence of an articulated reasoning with some rational underpinning to support the legal conclusion of obviousness and (2) one or more elements are missing from the cited combination.

Applicant submits that the rejection under 35 U.S.C. § 103(a) is improper for reasons of record as presented above with respect to the rejection of claims 1, 2, 4, and 17 over the Weiss patent in view of Sanberg and Grabowski. As stated above, "all words in a claim must be considered in judging the patentability of that claim against the prior art."[36] "If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious."[37] The courts have held that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."[38] Furthermore, one may rebut a prima facie case of obviousness by showing that the art, in any material respect, teaches away from the claimed invention.[39] "It is improper to combine references where the references teach away from their combination."[40]

Sanberg fails to teach administration of at least 6 million hNT cells to a plurality of brain

---

[36] See MPEP 2143.03 – All Claim limitations Must be Considered – *citing in re Wilson* " 'All words in a claim must be considered in judging the patentability of that claim against the prior art.' *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)."

[37] *In re Fine* 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

[38] MPEP 2143 citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) quoting In re Kahn, 441 F. 3d. 977, 988 (Fed. Cir. 2006).

[39] *In re Geisler,* 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

[40] MPEP 2145 – References Cannot Be Combined Where Reference Teaches Away from Their Combination – citing *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

sites in a human and Weiss and Uchida fail to resolve that deficiency

Claims 7, 10, 13, and 17 of the present application all recite administration of at least 6 million hNT cells to a plurality of brain sites. In contrast, as stated above with respect to the rejection of claims 1, 2, 4, and 17 over Weiss in view of Sanberg and Grabowski, while Sanberg teaches the administration of hNT cells, it does not teach the administration of at least 6 million cells to a human who has undergone stroke nor does it teach the administration to a plurality of brain sites. Weiss and Uchida similarly do not teach the administration of at least 6 million hNT cells to a human at a plurality of brain sites.

In addition, as explained above with respect to the rejection of claims 1, 2, 4, and 17, Weiss and Sanberg teach away from their combination and therefore cannot be combined to form the basis of an obviousness rejection. Given that none of the references teach the administration of at least 6 million cells to a plurality of brain sites in a human as well as for the reasons outlined above in response to the rejection of claims 1, 2, 4, and 17 over Weiss in view of Sanberg and Grabowski, the cited combination of references fails to teach all of the elements of the claims in question and thus there is no basis for a legal finding of obviousness. Claim 12 is dependent upon claim 10 and given that independent claim 10 is nonobvious for the foregoing reasons, claim 12 would similarly be nonobvious. Applicant therefore respectfully requests that the rejection of claims 7, 10, 12, 13, and 17 be withdrawn.

Sanberg fails to teach the administration of at least 6 million hNT cells to a plurality of sites in the central nervous system or the cerebral spinal fluid and Weiss and Uchida fail to resolve that deficiency

Claim 14 is directed to, "[a] method of improving sensory function in a person who has experienced stroke-induced brain damage which interferes with sensation, said method comprising delivering a sterile composition of at least 6 million hNT neuronal cells to a **plurality of sites of the central nervous system or to the cerebral spinal fluid**." (emphasis added) Neither Sanberg nor Weiss nor Uchida teaches the administration of cells to a plurality of sites in the central nervous system or cerebral spinal fluid. All of the references are directed to the administration of cells to the brain, not the entire central nervous system and not the cerebral spinal fluid. Also, as stated above, none of the references teach the administration of at least 6 million hNT cells. Given that the cited combination of references fails to teach each and

every element of the claims in question, there can be no finding of obviousness. Claim 16 is dependent on claim 14 and given that independent claim 14 is nonobvious for the foregoing reasons, claim 16 would similarly be nonobvious.

For the foregoing reasons it is submitted that the Office has not made a *prima facie* case of obviousness as required under 35 U.S.C. § 103(a). It is therefore respectfully requested that the rejection of claims 14 and 16 under 35 U.S.C. § 103(a) be withdrawn.

Sanberg fails to teach migration of cells and Weiss and Uchida fail to resolve that deficiency

Claim 15 is directed to "[a] method of improving sensory, motor or cognitive function in a person who has experienced brain damage due to a stroke which interferes with those functions, said method comprising delivering a sterile composition of at least 6 million hNT neuronal cells into a plurality of locations from which the hNT neuronal cells **migrate** to the damaged area." (emphasis added) Neither Sanberg nor Weiss teach migration of cells to the damaged areas. The Office uses the Uchida reference to overcome this deficiency, however Uchida is equivocal as to whether or not the cells migrate. Uchida states on page 207:

> "…**it cannot be ruled out that the distant cells were deposited at their sites during implantation**. Further studies by monitoring temporal and spatial alterations in cell migration in vivo are required to determine whether the mobile behavior of neural plate-derived cells in vitro is displayed also in the adult CNS environment." (emphasis added)

Uchida does not state definitively that the cells migrate but rather that the location of the remote cells may occur at implantation. It is also noteworthy that the experiments in Uchida were conducted *in vitro* as opposed to *in vivo*. In fact, Uchida states that *in vivo* studies are needed to actually determine if there is mobile behavior involved. Given that the combination of Sanberg in view of Weiss and Uchida fails to teach the element of migration as dictated in claim 15, in addition to the shortcomings of failing to teach administration of at least 6 million hNT cells into a plurality of locations as discussed previously, the cited references fail to render the present application obvious.

In conclusion, for the foregoing reasons, it is therefore respectfully requested that the Office withdraw the rejection of claims 7, 10, 12-17 and 19 under 35 U.S.C. § 103(a) as being unpatentable over Sanberg et al. (1996. Soc. Neurosci. Abstr. 22(1-3):578, abstract 232.9) in view of Weiss (U.S. Patent (5,851,832) and Uchida et al. (1995. Exp. Neurol 132:194-208).

Conclusion

For the reasons cited above, Applicant believes that claims 1-2, 4, 7, 10, 12-17 and 19 are patentable and in condition for allowance.

If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

Very respectfully,

SMITH & HOPEN

By: /michele l lawson/

Dated: May 6, 2009

Michele L. Lawson
USPTO Reg. No. 50,767
180 Pine Avenue North
Oldsmar, FL 34677
(813) 925-8525
Attorneys for Applicant

CERTIFICATE OF ELECTRONIC TRANSMISSION
(37 C.F.R. 1.8(a))

I HEREBY CERTIFY that this Amendment E is being electronically transmitted to the United States Patent and Trademark Office through EFS Web on May 6, 2009.

Date: May 6, 2009

/jessica powell/
Jessica Powell